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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,414	10/12/2001	Mads Norregaard-Madsen	10081.200-US	9980
25908	7590	10/01/2003	EXAMINER	
NOVOZYMES NORTH AMERICA, INC. 500 FIFTH AVENUE SUITE 1600 NEW YORK, NY 10110			MOORE, WILLIAM W	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,414	NORREGAARD-MADSEN ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,7-27,38,40,42-44, and 47 is/are pending in the application.
- 4a) Of the above claim(s) 3,4,10,16-24 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,7-9,11-15,25,26,38,40,42-44 and 47 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>5 & 6</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Preliminary Amendment

Applicant's Preliminary Amendment A, Paper No. 3 filed with the specification on October 12, 2001, has been entered, canceling the original claims 6, 28-37, 39, 41, 45,
5 and 46. Claims 1-5, 7-27, 38, 40, 42-44 and 47 are pending herein.

Information Disclosure Statement

The Information Disclosure Statements filed March 5 and July 8, 2002, comply with the provisions of 37 CFR 1.97. The examiner was informed in a telephonic inquiry made of Applicant's counsel that a document indicated in the latter information disclosure to be
10 WO 02/21760 had a number resulting from a typographical error and that the intended document was instead was WO 92/21760, which document was considered by the examiner and the erroneous indication has been corrected on the PTO-Form 1449 that accompanied the Information Disclosure filed July 8, 2002.

Election/Restrictions

15 Claims 1, 5, 7-9, 38, 40, 42-44 and 47 are generic to a plurality of disclosed, patentably distinct, species comprising subtilase variants having amino acid insertions in seven distinct regions of a subtilase defined by clauses (a) to (g) of claim 1, compositions comprising same and methods of use thereof, as well as nucleic acid sequences encoding the distinct subtilase variants, vectors and transformed host cells comprising the subtilase
20 variant-encoding nucleic acid sequences, and methods of making an encoded subtilase variant recombinantly using the transformed host cells. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

For purposes of restriction, six structurally distinct species are defined thus:

1. Species comprising at least one insertion between positions 42 and 43.
- 25 2. Species comprising at least one insertion between any of positions 51 and 56.
3. Species comprising at least one insertion between any of positions 155 and 161.
4. Species comprising at least one insertion between positions 187 and 190.
5. Species comprising at least one insertion between any of positions 216 and 218.
6. Species comprising at least one insertion between positions 218 and 219.

During a telephone conversation with Mr. Elias Lambiris on September 22, 2003, a provisional election was made with traverse to prosecute the invention of the species of subtilase variants comprising at least one amino acid insertion between any of the subtilisin BPN'-correspondent positions 51 through 56, clause (b) of claim 1 as well as claims 2 and 11-15. Applicant's verbal traversal on September 22, 2003, consisted of the request that the species of subtilase variants comprising at least one amino acid insertion between any of the subtilisin BPN'-correspondent positions 216 through 218 be examined as well. This was acceptable and species of subtilase variants comprising at least one amino acid insertion between any of the subtilisin BPN'-correspondent positions 216-218 were searched as well as species of subtilase variants comprising at least one amino acid insertion between any of the subtilisin BPN'-correspondent positions 51 through 56, and claims 1, 2, 5, 7-9, 11-15, 25, 26, 38, 40, 42-44, and 47 are examined herein to the extent that they describe the subtilase variant species of clauses (b), (e) and (f) of claim 1 and claims 2, 11-15, 25 and 26. Affirmation of this election must be made by applicant in replying to this Office action. Clauses (a), (c), (d), and (g) of claim 1 and claims 3, 4, 10, 16-24 and 27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103(a) of the other invention.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 5, 7-9, 11-15, 25, and 26 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter.

Claim 1 is directed to non-statutory subject matter because a subtilase variant, without further limitation such as, e.g., isolated and modified, indicating that the invention is the product of a person, is a product present in Nature where any naturally-occurring subtilase that differs in its amino acid sequence from another naturally-occurring subtilase is a "variant" thereof. Claims 2, 5, 7-9, 11-15, 25, and 26 are included in this rejection and similarly fail to describe a composition of matter distinct from a naturally-occurring product in Nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 7-9, 11-15, 25, 26, 38, 40, 42-44 and 47 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is agreed that the specification adequately describes the preparation of the five species of subtilase variants comprising amino acid sequence modifications that are insertions of one or more amino acids between any individual set of adjacent positions among the subtilisin BPN'-correspondent positions 51-56, according to clause (b) of claim 1 and claims 2 and 11-15 herein, as well as an adequate constructive description of (i) the ten species of subtilase variants comprising amino acid sequence modifications that are insertions of one or more amino acids between any two sets of adjacent positions among these six positions, (ii) the ten species of subtilase variants comprising amino acid sequence modifications that are insertions of one or more amino acids between any three sets of

Art Unit: 1652

adjacent positions among these six positions, and, (iii) the five species of subtilase variants comprising amino acid sequence modifications that are insertions of one or more amino acids between any four sets of adjacent positions among these six positions. It is further agreed that the specification provides an adequate written description of the preparation of species of subtilase variants meeting structural limitations of clauses (e) and (f) of claim 1 and claims 25 and 26 herein that have proteolytic activity and meet functional limitations of claim 5, see, e.g., Example 4, where they comprise insertions of single amino acids between either the subtilisin BPN'-correspondent positions 216 and 217 or 217 and 218.

The specification fails, however, to exemplify or describe the preparation of subject matters that are elected subtilase variants of clause (b) of claim 1 that are proteolytically active where they comprise insertions of multiple amino acid between one or more of the subtilisin BPN'-correspondent positions 51 and 56 or that meet the functional limitation of claim 5. Neither does the specification exemplify or describe the preparation of subject matters that are elected subtilase variants of clauses (e) and (f) of claim 1 that are active as proteases where they comprise multiple amino acid insertions between the subtilisin BPN'-correspondent positions 216 and 218, nor any such multiply-substituted subtilisin variants that meet the functional limitation of claim 5. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification provides no characteristic permitting a correlation between the exhibition of proteolytic activity in a variant, or a retained proteolytic acid in the Ovo-inhibitor assay of claim 5 in a variant, where subtilase amino acid sequences are modified by inserting multiple amino acids between one or more sets of adjacent positions among the subtilisin BPN'-correspondent positions 51-56, or between the subtilisin BPN'-

Art Unit: 1652

correspondent positions 126 and 128. The Court of Appeals for the Federal Circuit has also determined that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Yet nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of undisclosed subtilase variants having multiple amino acid insertions between one or more of the subtilisin BPN'-correspondent positions 51 and 56 or the subtilisin BPN'-correspondent positions 216 and 218 that still function as proteases, let alone meet the limitation of claim 5, to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)). The specification's treatment of the elected subject matters is considered to be entirely prospective where skilled artisans in the relevant field of subtilase modification could not predict the structures of the claimed subtilase variants comprising multiple amino acid insertions that retain proteolytic activity, or the degree of activity recited in claim 5.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 7-9, 11-15, 25, 26, 38, 40, 42-44, and 47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it fails to clearly identify the basis for numbering amino acid positions in the amino acid sequence of a generic subtilase where the elected amino acid insertions are to be made where the specification provides, see SEQ ID NO:7, the specific amino acid sequence of the mature subtilisin BPN' referred to at the close of claim

Art Unit: 1652

1. Claims 2, 5, 7-9, 11-15, 25, 26, 38, 40, 42-44, and 47 are included in this rejection because they depend from claim 1 but do not otherwise clearly identify the basis for numbering amino acid positions. Amending claim 1 to insert, after the term "subtilisin BPN'", the phrase, "set forth in SEQ ID NO:7", will overcome this rejection. Claim 5 is independently rejected as indefinite for its recitation of the phrase, "has a residual activity of at least 10% in the Ovo-inhibition assay" because it fails to indicate what Applicant intends in reciting "residual activity", i.e., a comparison of proteolytic activity between the unmodified and the modified protease, and because it fails to indicate the particulars of "the" Ovo-inhibition assay" where no such assay is described in a preceding claim.

Conclusion


While claims 1, 2, 5, 7-9, 11-15, 25, 26, 38, 40, 42-44, and 47 are rejected under one or more of 35 U.S.C. §§101 and 112, first and second paragraphs, above the elected subject matters described by these claims is allowable over the prior art made of record herewith. Christianson et al., WO 92/21760, which Applicant intended to make of record with the Information Disclosure filed July 8, 2002, disclose, e.g., at pages 15-17, only amino acid substitutions, and no insertions, at positions in a *Bacillus subtilisin* none of which correspond to any of the subtilisin BPN' positions 51-56 or 216-218. Christianson et al. do not suggest that any amino acid insertions be made in a subtilase amino acid sequence. Hansen et al., WO 99/27082, made of record with the Information Disclosure filed March 5, 2002, and the corresponding U.S. Patent to Hansen et al., U.S. 6,605,458, made of record herewith, commonly disclose amino acid insertions at numerous positions in the amino acid sequence of subtilases generally, but, see, e.g., pages 2-8 and 16-21 and claim 1 of Hansen et al., WO 99/27082, disclose no insertions at subtilisin BPN'-correspondent positions between positions 51 to 56 or between positions 216-218 and teach away from such insertions by choosing to make

Art Unit: 1652

their disclosed insertions at numerous other positions. Fano et al., WO 01/44452, make of record with the Information Disclosure filed July 8, 2002, disclose the Ovo-inhibitor assay taught in the instant application and also disclose amino acid insertions at subtilisin BPN'-correspondent positions between positions 216 and 217 and between positions 217 and 218, but cannot constitute prior art to an invention elected herein because the instant application claims priority to an October 17, 2000-filed U.S. provisional application, a filing date earlier than the December 2000 filing date of the application published as WO 01/44452, which traces no priority to any U.S. provisional application. Hansen et al., U.S. Patent No. 6,506,589, made of record herewith together with the published U.S. patent application US 2003/0148495 sharing a common disclosure, teach modification of the amino acid sequence of subtilisin 309 by an insertion of an amino acid at a position corresponding to position 56 in the amino acid sequence of the mature subtilisin BPN' but this is not a site for substitution claimed herein but an outer boundary within which a claimed insertion must be made, see, e.g., claim 2 herein, and the insertion in the amino acid sequence of subtilisin 309 replaces the relative lack of an amino acid at this subtilisin BPN'-correspondent in the shorter amino acid sequence of subtilisin 309.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
September 26, 2003


NASHAAT T. NASHED PHD
PRIMARY EXAMINER